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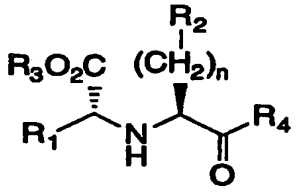
(54) Title: N-CARBOXYALKYL DERIVATIVES AS ANTIDEGENERATIVE ACTIVE AGENTS

(57) Abstract

Novel N-carboxyalkyl derivatives of formula (I) are found to be useful inhibitors of matrix metalloendoproteinase-mediated diseases including osteoarthritis, rheumatoid arthritis, septic arthritis, tumor invasion in certain cancers, periodontal disease, corneal ulceration, proteinuria, dystrophobic epidermolysis bullosa, coronary thrombosis associated with atherosclerotic plaque rupture, and aneurysmal aortic disease. The matrix metalloendoproteinases are a family of zinc-containing proteinases including but not limited to stromelysin, collagenase, and gelatinase, that are capable of degrading the major components of articular cartilage and basement membranes. The inhibitors claimed herein may also be useful in preventing the pathological sequelae following a traumatic injury that could lead to a permanent disability. These compounds may also have utility as a means for birth control by preventing ovulation or implantation.



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TITLE OF THE INVENTION

N-CARBOXYALKYL DERIVATIVES AS ANTIDEGENERATIVE ACTIVE AGENTS

BACKGROUND OF THE INVENTION

This application is directed to novel N-carboxyalkyl derivatives which are useful as inhibitors of matrix metalloendoproteinase and are useful in the treatment of matrix metalloendoproteinase-mediated diseases.

The disability observed in osteoarthritis (OA) and rheumatoid arthritis (RA) is largely due to the loss of articular cartilage. No therapeutic agent in the prior art is known to prevent the attrition of articular cartilage in these diseases.

"Disease modifying antirheumatic drugs" (DMARD's), i.e., agents capable of preventing or slowing the ultimate loss of joint function in OA and RA are widely sought. Generic nonsteroidal antiinflammatory drugs (NSAIDs) may be combined with such agents to provide some relief from pain and swelling.

Stromelysin (aka. proteoglycanase, matrix metalloproteinase-3 (MMP-3), procollagenase activator, "transin"), collagenase (aka. interstitial collagenase, matrix metalloproteinase-1 (MMP-1)), and gelatinase (aka. type IV collagenase, matrix metalloproteinase-2 (MMP-2), 72kDa-gelatinase or type V collagenase, matrix metalloproteinase-9, (MMP-9), 92kDa-gelatinase) are metalloendoproteinases secreted by fibroblasts and chondrocytes, and are capable of degrading the major connective tissue components of articular cartilage or basement membranes. Elevated levels of both enzymes have been detected in joints of arthritic humans and animals: K.A. Hasty, R.A. Reife, A.H. Kang, J.M. Stuart, "The role of stromelysin in the cartilage destruction that accompanies inflammatory arthritis", Arthr. Rheum., 33, 388-97 (1990); S.M. Krane, E.P. Amento, M.B. Goldring, S.R. Goldring, and M.L. Stephenson, "Modulation of matrix synthesis and degradation in joint inflammation", The Control of Tissue Damage, A.B. Glauert (ed.), Elsevier Sci. Publ.,

Amsterdam, 1988, Ch. 14, pp 179-95; A. Blanckaert, B. Mazieres, Y. Eeckhout, G. Vaes, "Direct extraction and assay of collagenase from human osteoarthritic cartilage", Clin. Chim. Acta, 185 73-80 (1989). Each enzyme is secreted from these cells as an inactive proenzyme which is subsequently activated. There is evidence that stromelysin may be the *in vivo* activator for collagenase, implying a cascade for degradative enzyme activity: A. Ho, H. Nagase, "Evidence that human rheumatoid synovial matrix metalloproteinase 3 is an endogenous activator of procollagenase", Arch Biochem Biophys., 267, 211-16 (1988); G. Murphy, M.I. Crockett, P.E. Stephens, B.J. Smith, A.J.P. Docherty, "Stromelysin is an activator of procollagenase", Biochem. J., 248, 265-8 (1987); Y. Ogata, J.J. Engh. ld, H. Nagase, "Matrix metalloprotease-3 (stromelysin) activates the precusor for human matrix metalloproteinase-9," J. Biol. Chem. 267, 3581-84 (1992). Inhibiting stromelysin could limit the activation of collagenase and gelatinase as well as prevent the degradation of proteoglycan.

That stromelysin inhibition may be effective in preventing articular cartilage degradation has been demonstrated in vitro by measuring the effect of matrix metalloendoproteinase inhibitors on proteoglycan release from rabbit cartilage explants: C.B. Caputo, L.A. Sygowski, S.P. Patton, D.J. Wolanin, A. Shaw, R.A. Roberts, G. DiPasquale, J. Orthopaedic Res., 6, 103-8 (1988).

There is an extensive literature on the involvement of these metalloproteinases in arthritis, but there is very little to guide one in developing a specific inhibitor for each enzyme.

In preliminary studies of rabbit proteoglycanase with substrates and inhibitors, little was found to indicate the enzyme's requirements for hydrolysis or inhibition beyond a preference for hydrophobic residues at the P_1' position: A. Shaw, R.A. Roberts, D.J. Wolanin, "Small substrates and inhibitors of the metalloproteoglycanase of rabbit articular chondrocytes", Adv. Inflam. Res., 12, 67-79 (1988). More extensive studies with a series of substrates and inhibitors revealed that stromelysin will tolerate nearly every amino acid residue around the scissile bond: S.J. Netzel-Arnett, G.B. Fields, H. Nagase, K. Suzuki,

W.G.I. Moore, H. Brikedal-Hansen, H.E. Van Wart, "Comparative sequence Specificities of human fibroblast and Neutrophil matrix metalloproeinases and inhibitors" -- Matrix supplement No. 1; H. Brikedal-Hansen, Z. Werk, H.E. Van Wart, Eds.; Gustov Fisher Verlag:New York 1992; K.T. Chapman, I.E. Kopka, P.L. Durette, C. K. Esser, T.J. Lanza, M. Izquierdo-Martin, L. Niedzwiecki, B. Chang, R.K. Harrison, D.W. Kuo, T.-Y. Lin, R.L. Stein, W.K. Hagmann, J. Med. Chem. 36, 4293-4301 (1993).

Human rheumatoid synovial collagenase has been shown to share ~ 50% homology with human stromelysin: S.E. Whitham, G. Murphy, P. Angel, H.J. Rahmsdorf, B.J. Smith, A. Lyons, T.J.R. Harris, J.J. Reynolds, P. Herrlich, A.J.P. Docherty, "Comparison of human stromelysin and collagenase by cloning and sequence analysis", Biochem. J., 240, 913-6 (1986). Many collagenase inhibitors have been designed around the cleavage site of the α-chain sequence of Type II collagen: W.H. Johnson, N.A. Roberts, N. Brokakoti, "Collagenase inhibitors: their design and potential therapeutic use", J. Enzyme Inhib., 2,1-22 (1987); M.A. Schwartz and H.E. Van Wart, "Synthetic Inhibitors of Bacterial and Mammalian Interstitial Collagenases", In Prog. Med. Chem. vol. 29; G.P. Ellis and D.K. Luscombe, Eds.; Elsevier Sc. Publ.; 1992; Ch 8, pp 271-334.

Gelatinase (MR ~ 72,000) has been isolated from rheumatoid fibroblasts: Y. Okada, T. Morodomi, J.J. Enghild, K. Suzuki, A. Yasui, I. Nakanishi, G. Salvesen, H. Nagase, "Matrix metalloproteinase 2 from human rheumatoid synovial fibroblasts", Eur. J., Biochem., 194, 721-30 (1990). The synthesis of the proenzyme is not coordinately regulated with the other two metalloproteinases and its activation may also be different. The role of gelatinase in the tissue destruction of articular cartilage appears different from the other two enzymes and, therefore, its inhibition may provide additional protection from degradation. A higher molecular weight gelatinase (MR ~ 92,000; aka. type-V collagenase, matrix metalloproteinase-9, MMP-9) is also secreted by fibroblasts and monocytes and may be involved in cartilage degradation: M. Mohtai, R.L. Smith, D.J. Schurman, Y. Tsuji, F.M.

Torti, N.I. Hutchinson, W.G. Stetler-Stevenson, G.I. Goldberg "Expression of 92-kD Type IV Collagenase/Gelatinase (Gelatinase B) in Osteoarthritic Cartilage and Its Induction in Normal Articular Cartilage by Interleukin 1", J. Clin. Invest. 92, 179-185 (1993).

The significant proportion of homology between human fibroblast collagenase, stromelysin, and gelatinase leads to the possibility that a compound that inhibits one enzyme may to some degree inhibit all of them.

Compounds that inhibit collagenase, which possess structural portions akin to those of the instant invention include those encompassed by U.S. 4,511,504, U.S. 4,568,666, EPO 520,573A1, PCT WO94/00119A, and EPO 126974 Al.

Compounds of related structure that are claimed to inhibit stromelysin (proteoglycanase) are encompassed by U.S. 4,771,037, and PCT WO92/21360A,

Stromelysin and collagenase inhibitors are believed to have utility in preventing articular cartilage damage associated with septic arthritis. Bacterial infections of the joints can elicit an inflammatory response that may then be perpetuated beyond what is needed for removal of the infective agent resulting in permanent damage to structural components. Bacterial agents have been used in animal models to elicit an arthritic response with the appearance of proteolytic activities. See J.P. Case, J. Sano, R. Lafyatis, E.F. Remmers, G.K. Kumkumian, R.L. Wilder, "Transin/stromelysin expression in the synovium of rats with experimental erosive ~~arhtritis~~ arthritis", J. Clin Invest., 84, 1731-40 (1989); R.J. Williams, R.L. Smith, D.J. Schurman, "Septic Arthritis: Staphylococcal induction of chondrocyte proteolytic activity", Arthr. Rheum., 33, 533-41 (1990).

Inhibitors of stromelysin, collagenase, and gelatinase are believed to be useful to control tumor metastasis, optionally in combination with current chemotherapy and/or radiation. See L.M. Matrisian, G.T. Bowden, P. Krieg, G. Furstenberger, J.P. Briand, P. Leroy, R. Breathnach, "The mRNA coding for the secreted protease transin is expressed more abundantly in malignant than in benign

tumors", Proc. Natl. Acad. Sci., USA, 83, 9413-7 (1986); S.M. Wilhelm, I.E. Collier, A. Kronberger, A.Z. Eisen, B.L. Marmer, G.A. Grant, E.A. Bauer, G. I. Goldberg, "Human skin fibroblast stromelysin: structure, glycosylation, substrate specificity, and differential expression in normal and tumorigenic cells", Ibid., 84, 6725-29 (1987); Z. Werb et al., "Signal transduction through the fibronectin receptor induces collagenase and stromelysin gene expression", J. Cell Biol., 109, 872-889 (1989); L.A. Liotta, C.N. Rao, S.H. Barsky, "Tumor invasion and the extracellular matrix", Lab. Invest., 49, 636-649 (1983); R. Reich, B. Stratford, K. Klein, G. R. Martin, R. A. Mueller, G. C. Fuller, "Inhibitors of collagenase IV and cell adhesion reduce the invasive activity of malignant tumor cells", in Metastasis: Ciba Foundation Symposium; Wiley, Chichester, 1988, pp. 193-210.

Secreted proteinases such as stromelysin, collagenase, and gelatinase play an important role in processes involved in the movement of cells during metastasic tumor invasion. Indeed, there is also evidence that the matrix metalloproteinases are overexpressed in certain metastatic tumor cell lines. In this context, the enzyme functions to penetrate underlying basement membranes and allow the tumor cell to escape from the site of primary tumor formation and enter circulation. After adhering to blood vessel walls, the tumor cells use these same metalloendoproteinases to pierce underlying basement membranes and penetrate other tissues, thereby leading to tumor metastasis. Inhibition of this process would prevent metastasis and improve the efficacy of current treatments with chemotherapeutics and/or radiation.

These inhibitors should also be useful for controlling periodontal diseases, such as gingivitis. Both collagenase and stromelysin activities have been isolated from fibroblasts isolated from inflammed gingiva: V.J. Uitto, R. Applegren, P.J. Robinson, "Collagenase and neutral metalloproteinase activity in extracts of inflammed human gingiva", J. Periodontal Res., 16, 417-424(1981). Enzyme levels have been correlated to the severity of gum disease: C.M. Overall, O.W. Wiebkin, J.C. Thonard, "Demonstration of tissue

collagenase activity *in vivo* and its relationship to inflammation severity in human gingiva", J. Periodontal Res., 22, 81-88 (1987).

Proteolytic processes have also been observed in the ulceration of the cornea following alkali burns: S.I. Brown, C.A. Weller, H.E. Wasserman, "Collagenolytic activity of alkali-burned corneas", Arch. Opthalmol., 81, 370-373 (1969). Mercapto-containing peptides do inhibit the collagenase isolated from alkali-burned rabbit cornea: F.R. Burns, M.S. Stack, R.D. Gray, C.A. Paterson, Invest. Opthalmol., 30, 1569-1575 (1989). Treatment of alkali-burned eyes or eyes exhibiting corneal ulceration as a result of infection with inhibitors of these metalloendoproteinases in combination with sodium citrate or sodium ascorbate and/or antimicrobials may be effective in preventing developing corneal degradation.

Stromelysin has been implicated in the degradation of structural components of the glomerular basement membrane (GBM) of the kidney, the major function of which is to restrict passage of plasma proteins into the urine; W.H. Baricos, G. Murphy, Y. Zhou, H.H. Nguyen, S.V. Shah, "Degradation of glomerular basement membrane by purified mammalian metalloproteinases", Biochem. J., 254, 609-612 (1988). Proteinuria, a result of glomerular disease, is excess protein in the urine caused by increased permeability of the GBM to plasma proteins. The underlying causes of this increased GBM permeability are unknown, but proteinases including stromelysin may play an important role in glomerular diseases. Inhibition of this enzyme may alleviate the proteinura associated with kidney malfunction.

Inhibition of stromelysin activity may prevent the rupturing of atherosclerotic plaques leading to coronary thrombosis. The tearing or rupture of atherosclerotic plaques is the most common event initiating coronary thrombosis. Destabilization and degradation of the connective tissue matrix surrounding these plaques by proteolytic enzymes or cytokines released by infiltrating inflammatory cells has been proposed as a cause of plaque fissuring. Such tearing of these plaques can cause an acute thrombolytic event as blood rapidly flows out of the blood vessel. High levels of stromelysin RNA message have been

found to be localized to individual cells in atherosclerotic plaques removed from heart transplant patients at the time of surgery: A.M. Henney, P.R. Wakeley, M.J. Davies, K. Foster, R. Hembry, G. Murphy, S. Humphries, "Localization of stromelysin gene expression in atherosclerotic plaques by *in situ* hybridization", Proc. Nat'l. Acad. Sci. USA, **88**, 8154-8158 (1991). Inhibition of stromelysin by these compounds may aid in preventing or delaying the degradation of the connective tissue matrix that stabilizes the atherosclerotic plaques, thereby preventing events leading to acute coronary thrombosis.

It is also believed that inhibitors of matrix metalloproteinases would have utility in treating degenerative aortic disease associated with thinning of the medial aortic wall. Aneurysms are often associated with atherosclerosis in this tissue. Increased levels of the degradative activities of the matrix metalloproteinases have been identified in patients with aortic aneurysms and aortic stenosis: N. Vine, J.T. Powell, "Metalloproteinases in degenerative aortic diseases", Clin. Sci., 81, 233-9 (1991). Inhibition of these enzymes may aid in preventing or delaying the degradation of aortic tissue, thus preventing events leading to acute and often times fatal aortic aneurysms.

It is also believed that specific inhibitors of stromelysin and collagenase should be useful as birth control agents. There is evidence that expression of metalloendoproteinases, including stromelysin and collagenase, is observed in unfertilized eggs and zygotes and at further cleavage stages and increased at the blastocyst stage of fetal development and with endoderm differentiation: C.A. Brenner, R.R. Adler, D.A. Rappolee, R.A. Pedersen, Z. Werb, "Genes for extracellular matrix-degrading metalloproteinases and their inhibitor, TIMP, are expressed during early mammalian development", Genes & Develop., 3, 848-59 (1989). By analogy to tumor invasion, a blastocyst may express metalloproteinases in order to penetrate the extracellular matrix of the uterine wall during implantation. Inhibition of stromelysin and collagenase during these early developmental processes should presumably prevent normal embryonic development and/or implantation in the uterus. Such intervention would constitute a novel

method of birth control. In addition there is evidence that collagenase is important in ovulation processes. In this example, a covering of collagen over the apical region of the follicle must be penetrated in order for the ovum to escape. Collagenase has been detected during this process and an inhibitor has been shown to be effective in preventing ovulation: J.F. Woessner, N. Morioka, C. Zhu, T. Mukaida, T. Butler, W.J. LeMaire "Connective tissue breakdown in ovulation", Steroids, 54, 491-499 (1989). There may also be a role for stromelysin activity during ovulation: C.K.L. Too, G.D. Bryant-Greenwood, F.C. Greenwood, "Relaxin increases the release of plasminogen activator, collagenase, and proteo-glycanase from rat granulosa cells *in vitro*", Endocrin., 115, 1043-1050 (1984).

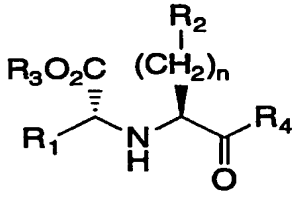
Collagenolytic and stromelysin activity have also been observed in dystrophobic epidermolysis bullosa: A. Kronberger, K.J. Valle, A.Z. Eisen, E.A. Bauer, J. Invest. Dermatol., 79 208-211 (1982); D. Sawamura, T. Sugawara, I. Hashimoto, L. Bruckmer-Tuderman, D. Fujimoto, Y. Okada, N. Utsumi, H. Shikata, Biochem. Biophys. Res. Commun., 174, 1003-8 (1991). Inhibition of metalloendoproteinases should limit the rapid destruction of connective components of the skin.

In addition to extracellular matrix comprising structural components, stromelysin can degrade other *in vivo* substrates including the inhibitors α_1-proteinase inhibitor and may therefore influence the activities of other proteinases such as elastase: P. G. Winyard, Z. Zhang, K. Chidwick, D. R. Blake, R. W. Carrell, G. Murphy, "Proteolytic inactivation of human α_1-antitrypsin by human stromelysin", FEBS Letts., 279, 1, 91-94 (1991). Inhibition of the matrix metalloendoproteinases may potentiate the antiproteinase activity of these endogenous inhibitors.

SUMMARY OF THE INVENTION

The invention encompasses novel N-carboxyalkyl derivatives of Formula I which are useful as inhibitors of matrix metalloendoproteinase and are useful in the treatment of matrix

metalloendoproteinase mediated diseases including degenerative diseases (such as defined above) and certain cancers.



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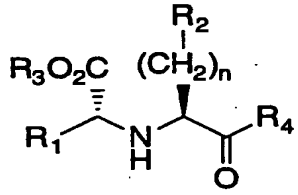
DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the invention encompasses a compound of Formula I



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or a pharmaceutically acceptable salt thereof wherein:

R_1 is hydrogen, substituted C_{1-6}alkyl, or substituted C_{2-6} alkenyl wherein the substituent is selected from the group consisting of:

(a) hydrogen,
(b) carboxy,
(c) aminocarbonyl,
(d) C1-6alkoxy,
(e) C1-6alkylthio,
(f) C1-6alkylsulfonyl,
(g) C1-6alkylcarbonyl,
(h) C_{1-6}alkylcarbonyl,

(i) aryl wherein the aryl is selected from the group consisting of:

(1) phenyl,
(2) naphthyl,
(3) pyridyl,
(4) furyl,
(5) pyrryl,
(6) thienyl,
(7) isothiazolyl,
(8) imidazolyl,
(9) benzimidazolyl,
(10) tetrazolyl,
(11) pyrazinyl,
(12) pyrimidyl,
(13) quinolyl,
(14) isoquinolyl,
(15) benzofuryl,
(16) isobenzofuryl,
(17) benzothienyl,
(18) pyrazolyl,
(19) indolyl,
(20) isoindolyl,
(21) purinyl,
(22) carbazolyl,
(23) isoxazolyl,
(24) thiazolyl,
(25) oxazolyl,
(26) benzthiazolyl, and
(27) benzoxazolyl,

optionally mono and di-substituted with substituents independently selected from C_{1-6}alkyl, C_{1-6}alkyl-oxy, halo, hydroxy, amino, C_{1-6}alkylamino, aminoC_{1-6}alkyl, carboxyl, carboxylC_{1-6}alkyl, and C_{1-6}alkylcarbonyl;

(j) aryloxy wherein aryl is defined in item (i) immediately above,

(k) aroyl wherein aryl is defined in item (i) immediately above,

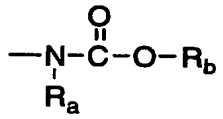
(l) amino or mono- or di-substituted amino wherein the substituents are independently selected from C_{1-6} alkyl and aryl as defined (i) immediate above,

(m) arylthio wherein aryl is defined in item (i) immediately above,

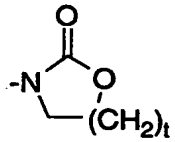
(n) arylsulfinyl wherein aryl is defined in item (i) immediately above,

(o) arylsulfonyl wherein aryl is defined in item (i) immediately above,

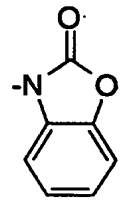
(p)



wherein R_a and R_b are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its substituents are as defined in (i) above, or
wherein Ra and Rb are joined together with the nitrogen and oxygen atoms to which they are attached to form a saturated or unsaturated cyclic-urethane, or a saturated or unsaturated benzofused cyclic-urethane, wherein the urethane ring contains 5, 6, 7, or 8 atoms, said ring containing two heteroatoms N and O such as;



wherein t is 1, 2 or 3,
or



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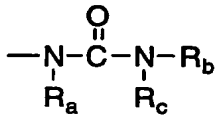
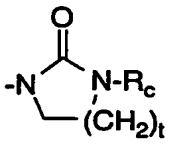
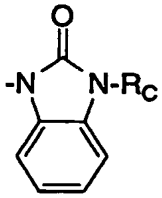


wherein R_a R_b, and R_c are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its substituents areas defined in (i) above, or
wherein Ra and Rb are joined together with the nitrogen atoms to which they are attached to form a saturated or unsaturated cyclic-urea or saturated or unsaturated benzofused cyclic-urea, said urea ring containing 5, 6, 7, or 8 atoms and two heteroatoms which are nitrogens such as;



wherein t is 1, 2 or 3,
or



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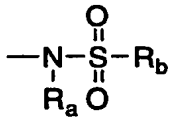
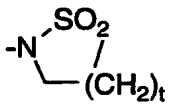
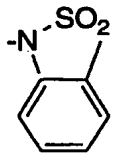


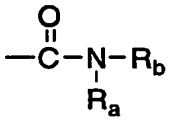
wherein R_a and R_b are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its substituents areas defined in (i) above, or
wherein Ra and Rb are joined together with the nitrogen and sulfur atoms to which they are attached, to form a saturated or unsaturated cyclic-sulfonamide or saturated or unsaturated benzofused cyclic-sulfonamide ring, said sulfonamide ring containing 5, 6, 7, or 8 atoms and two heteroatoms which are N and S such as ;



wherein t is 1, 2 or 3,
or

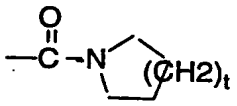


(s)



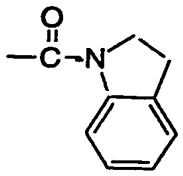
wherein R_a and R_b are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its substituents areas defined in (i) above, or

wherein Ra and Rb are joined together with the nitrogen atom to which they are attached, to form a saturated or unsaturated heterocycle or staurated or unsaturated benzofused heterocycle ring, said ring containing 5, 6, 7, or 8 atoms and a heteroatom which is nitrogen such as;

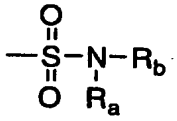


wherein t is 1, 2 or 3,

or

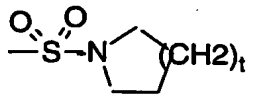


(t)

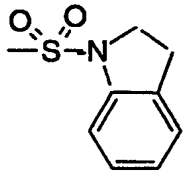


wherein R_a and R_b are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its substituents areas defined in (i) above, or

wherein Ra and Rb are joined together with the nitrogen atom to which they are attached, to form a saturated or unsaturated heterocycle or saturated or unsaturated benzofused heterocycle ring, said ring containing 5, 6, 7, or 8 atoms including a heteroatom which is nitrogen such as,



wherein t is 1, 2 or 3,
or



R_2 is biaryl wherein the aryl group is selected from the group consisting of:

(1) phenyl,
(2) naphthyl,
(3) pyridyl,
(4) pyrryl,
(5) furyl,
(6) thienyl,
(7) isothiazolyl,
(8) imidazolyl,
(9) benzimidazolyl,
(10) tetrazolyl,
(11) pyrazinyl,
(12) pyrimidyl,
(13) quinolyl,
(14) isoquinolyl,
(15) benzofuryl,
(16) isobenzofuryl,
(17) benzothienyl,
(18) pyrazolyl,
(19) indolyl,
(20) isoindolyl,
(21) purinyl,

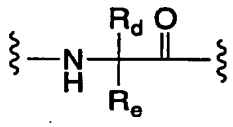
(22) carboxazolyl,
(23) isoxazolyl,
(24) thiazolyl,
(25) oxazolyl,
(26) benzthiazolyl, and
(27) benzoxazolyl,

optionally mono or di-substituted with substitutents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo, haloalkyl, hydroxy, amino, C_{1-6}alkylamino, aminoC_{1-6}alkyl, aminosulfonyl, aminocarbonyl, ureido, sulfonylureido, C_{1-6}alkoxycarbonyl, carboxyl, carboxylC_{1-6}alkyl, and C_{1-6}alkylcarbonyl;

R_3 is

(a) H,
(b) Z, where Z is a pharmaceutically acceptable counterion,
(c) C_{1-10}alkyl,
(d) aryl or aryl C_{1-3}alkyl, wherein the aryl group is selected from the group consisting of
  (1) phenyl, and
  (2) substituted phenyl, wherein the substitutent is carboxy, carboxyC_{1-3}alkyl, aminocarbonyl, C_{1-6}alkylaminocarbonyl;

R_4 is X-R_5 wherein X is a single bond or an amino acid of formula **II**



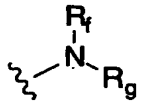
II

wherein R_d and R_e are individually selected from:

(a) hydrogen,

(b) C_{1-6}alkyl,
(c) mercapto C_{1-6}alkyl,
(d) hydroxy C_{1-6}alkyl,
(e) carboxy C_{1-6}alkyl,
(f) amino substituted C_{2-6}alkyl
(g) aminocarbonyl C_{1-6}alkyl,
(h) mono- or di-C_{1-6}alkyl amino C_{2-6}alkyl,
(i) guanidino C_{2-6}alkyl,
(j) substituted phenyl C_{1-6}alkyl, wherein the substitutent is hydrogen,hydroxy, carboxy, C_{1-4} alkyl, or C_{1-4}alkyloxy,
(k) substituted indolyl C_{1-6}alkyl, wherein the substitutent is hydrogen, hydroxy, carboxy, C_{1-4} alkyl, or C_{1-4}alkyloxy,
(l) substituted imidazolyl C_{2-6}alkyl wherein the substitutent is hydrogen, hydroxy, carboxy, C_{1-4} alkyl, or C_{1-4}alkyloxy,
(m) substituted pyridyl C_{1-6}alkyl wherein the substitutent is hydrogen, hydroxy, carboxy, C_{1-4} alkyl, or C_{1-4}alkyloxy,
(n) substituted pyridylamino C_{1-6}alkyl wherein the substitutent is hydrogen, hydroxy, carboxy, C_{1-4} alkyl, or C_{1-4}alkyloxy,
(o) substituted pyrimidinyl C_{1-6}alkyl wherein the substitutent is hydrogen, hydroxy, carboxy, C_{1-4} alkyl, or C_{1-4}alkyloxy,

R_5 is



wherein R_f and R_g are each individually selected from the group consisting of:
(a) H,
(b) substituted C_{1-10}alkyl wherein the substituents are independently selected from hydrogen, C_{1-6}alkyloxy,

hydroxy, halo, amino, C_{1-6}alkylamino, carboxyl, and C_{1-6}alkylcarbonyl;

(c) Aryl or arylC_{1-6}alkyl, wherein the aryl group is selected from the group consisting of

(1) phenyl,
(2) naphthyl,
(3) pyridyl,
(4) pyrryl,
(5) furyl,
(6) thienyl,
(7) isothiazolyl,
(8) imidazolyl,
(9) benzimidazolyl,
(10) tetrazolyl,
(11) pyrazinyl,
(12) pyrimidyl,
(13) quinolyl,
(14) isoquinolyl,
(15) benzofuryl,
(16) isobenzofuryl,
(17) benzothienyl,
(18) pyrazolyl,
(19) indolyl,
(20) isoindolyl,
(21) purinyl,
(22) carbazolyl,
(23) isoxazolyl,
(24) benzthiazolyl,
(25) benzoxazolyl,
(26) thiazolyl, and
(27) oxazolyl.

optionally mono or di-substituted with substitutents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl,

halo, haloalkyl, hydroxy, amino, C_{1-6}alkylamino, aminoC_{1-6}alkyl, aminosulfonyl, aminocarbonyl, ureido, sulfonylureido, C_{1-6}alkoxycarbonyl, carboxyl, carboxylC_{1-6}alkyl, and C_{1-6}alkylcarbonyl;or

(d) R_f and R_g are joined together with the nitrogen atom to which they are attached, to form a heterocycle ring, wherein the heterocycle is selected from the group consisting of

(1) morpholine,
(2) thiomorpholine,
(3) thiomorpholine sulfone,
(4) pyrrolidine,
(5) piperazine,
(6) piperidine,
(7) 3-ketopiperazine, and
(8) 2-ketopiperazine;

optionally mono or di-substituted with substitutents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, halo, hydroxy, amino, C_{1-6}alkylamino, carboxyl, carboxylC_{1-6}alkyl, and C_{1-6}alkylcarbonyl.

For purposes of this specification, and as appreciated by those of skill in the art, the unsaturated rings such as those described in definitions R_1 (p), (q), (r), (s), and (t) are intended to include rings wherein a double bond is present at one, two or more of the available positions.

For purposes of this specification biaryl such as in definition R_2 is intended to include identical aryl groups, such as biphenyls, and heterogenous biaryls, such as furyl-phenyl, and substituted biaryls, such as p-phenyl-naphthyl or phenyl-(3-methyl-naphthyl).

Pharmaceutically acceptable counter-ions include those from salts of inorganic bases such as aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium. These counter-ions also include those from salts derived from

pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N_-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

One genus of this embodiment concerns compounds wherein:

n = 2-3; and

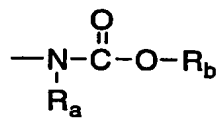
R_1 is hydrogen or mono- or di-substituted C_{1-6}alkyl wherein the substituents are independently selected from the group consisting of:

(a) hydrogen,
(b) C_{1-6}alkoxy,
(c) aryl group selected from the group consisting of:
  (1) phenyl,
  (2) naphthyl,
  (3) pyridyl,
  (4) pyrryl,
  (5) furyl,
  (6) thienyl,
  (7) isothiazolyl,
  (8) imidazolyl,
  (9) benzimidazolyl,
  (10) tetrazolyl,
  (11) pyrazinyl,
  (12) pyrimidyl,
  (13) quinolyl,

(14) isoquinolyl,
(15) benzofuryl,
(16) isobenzofuryl,
(17) benzothienyl,
(18) pyrazolyl,
(19) indolyl,
(20) isoindolyl,
(21) purinyl,
(22) carboxazolyl,
(23) isoxazolyl,
(24) thiazolyl,
(25) oxazolyl,
(26) benzthiazolyl, and
(27) benzoxazolyl,

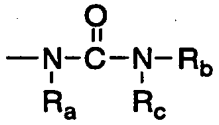
optionally mono- or di-substituted with substitutents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, chloro, fluoro, bromo, hydroxy, amino, C_{1-6}alkylamino, aminoC_{1-6}alkyl, carboxyl, carboxylC_{1-6}alkyl, or C_{1-6}alkylcarbonyl,

(d)



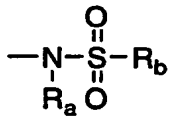
wherein R_a and R_b are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its optional substituents are as defined in (c) above, or
wherein Ra and Rb are joined together with the nitrogen and oxygen atoms to which they are attached to form a saturated or unsaturated cyclic-urethane, or a saturated or unsaturated benzofused cyclic-urethane, wherein the urethane ring contains 5, 6, 7, or 8 atoms, said ring containing two heteroatoms N and O;

(e)



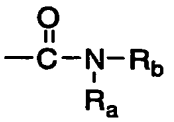
wherein R_a R_b, and R_c are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its optional substituents areas defined in (c) above, or
wherein Ra and Rb are joined together with the nitrogen atoms to which they are attached to form a saturated or unsaturated cyclic-urea or saturated or unsaturated benzofused cyclic-urea, said urea ring containing 5, 6, 7, or 8 atoms and two heteroatoms which are nitrogens;

(f)



wherein R_a and R_b are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its optional substituents areas defined in (c) above, or
wherein Ra and Rb are joined together with the nitrogen and sulfur atoms to which they are attached, to form a saturated or unsaturated cyclic-sulfonamide or saturated or unsaturated benzofused cyclic-sulfonamide ring, said sulfonamide ring containing 5, 6, 7, or 8 atoms and two heteroatoms which are N and S;

(g)



wherein R_a and R_b are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its optional substituents areas defined in (c) above, or

wherein Ra and Rb are joined together with the nitrogen atom to which they are attached, to form a saturated or unsaturated heterocycle or staurated or unsaturated benzofused heterocycle ring, said ring containing 5, 6, 7, or 8 atoms and a heteroatom which is nitrogen.

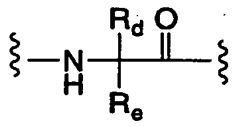
Within this sub-class are the compounds wherein

R_2 is biaryl wherein the aryl group is selected from the group consisting of:

(1) phenyl,
(2) naphthyl,
(3) thienyl,
(4) imidazolyl,
(5) pyrimidyl,
(6) benzofuryl,
(7) pyridyl,
(8) benzothienyl,

optionally mono or di-substituted with substitutents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo, haloalkyl, hydroxy, amino, C_{1-6}alkylamino, aminoC_{1-6}alkyl, aminosulfonyl, aminocarbonyl, ureido, sulfonylureido, C_{1-6}alkoxycarbonyl, carboxyl, carboxylC_{1-6}alkyl, and C_{1-6}alkylcarbonyl.

R_4 is X-R_5 wherein X is a single bond or an amino acid of formula **II**

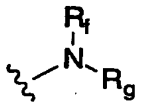


II

wherein R_d and R_e are individually selected from:

(a) hydrogen,
(b) C_{1-4}alkyl,
(c) mercapto C_{1-3}alkyl,
(d) hydroxy C_{1-4}alkyl,
(e) carboxy C_{1-4}alkyl,
(f) amino substituted C_{2-4}alkyl
(g) aminocarbonyl C_{1-4}alkyl,
(h) mono- or di-C_{1-4}alkyl amino C_{2-4}alkyl,
(i) guanidino C_{2-4}alkyl,
(j) substituted phenyl C_{1-4}alkyl, wherein the substitutent is hydrogen,hydroxy, carboxy, C_{1-3} alkyl, or C_{1-3}alkyloxy,
(k) substituted indolyl C_{1-3}alkyl, wherein the substitutent is hydrogen, hydroxy, carboxy, C_{1-3}alkyl, or C_{1-3}alkyloxy,
(l) substituted imidazolyl C_{2-4}alkyl wherein the substitutent is hydrogen, hydroxy, carboxy, C_{1-3} alkyl, or C_{1-3}alkyloxy,

R_5 is



wherein R_f and R_g are each individually selected from the group consisting of:

(a) H,
(b) substituted C_{1-6}alkyl wherein the substituents are independently selected from hydrogen, C_{1-4}alkyloxy, hydroxy, chloro, fluoro, bromo, amino, C_{1-4}alkylamino, carboxyl, and C_{1-4}alkylcarbonyl;

(c) aryl or arylC1-6alkyl, wherein the aryl group is selected from the group consisting of
(1) phenyl,
(2) naphthyl,
(3) pyridyl,
(4) thienyl,
(5) tetrazolyl,
(6) pyrazinyl,
(7) pyrimidyl,
(8) benzofuryl,
(9) benzothienyl,
(10) pyrazolyl,
(11) indolyl,

optionally mono or di-substituted with substitutents independently selected from C1-4alkyl, C1-4alkyloxy, hydroxyC1-4alkyl, C1-4alkoxyC1-4alkyl, fluoro, chloro, bromo, hydroxy, amino, C1-4alkylamino, aminoC1-4alkyl, carboxyl, carboxylC1-4alkyl, and C1-4alkylcarbonyl.

A smaller group within this group are the compounds wherein:

R3 is
(a) H,
(b) Z, where Z is a pharmaceutically acceptable counterion,
(c) C1-4alkyl,
(d) aryl or aryl C1-3alkyl, wherein the aryl group is selected from the group consisting of
(1) phenyl, and
(2) substituted phenyl, wherein the substitutent is carboxy, carboxyC1-3alkyl, aminocarbonyl.

R2 is arylC1-4alkyl, or biarylC1-4alkyl wherein the aryl group is selected from the group consisting of phenyl, thienyl, pyridyl, or naphthyl.

Exemplifying the present invention is the following compounds: N-[1(R)-Carboxyethyl]-α-(S)-2-(4-fluorobiphenyl)-glycyl-(S)-2-(tert-butyl)glycine, N-Phenyl Amide.

This invention also concerns pharmaceutical composition and methods of treatment of stromelysin-mediated or implicated disorders or diseases (as described above) in a patient (which shall be defined to include man and/or mammalian animals raised in the dairy, meat, or fur industries or as pets) in need of such treatment comprising administration of the stromelysin inhibitors of Formula I as the active constituents.

Similarly, this invention also concerns pharmaceutical compositions and methods of treatment of collagenase mediated or implicated disorders or diseases (as described above) in a patient in need of such treatment comprising administration of the collagenase inhibitors of Formula (I) as the active constituents.

Similarly, this invention also concerns pharmaceutical compositions and methods of treatment of gelatinase-mediated or implicated disorders or diseases (as described above) in a patient in need of such treatment comprising administration of the gelatinase inhibitors of Formula (I) as the active constituents.

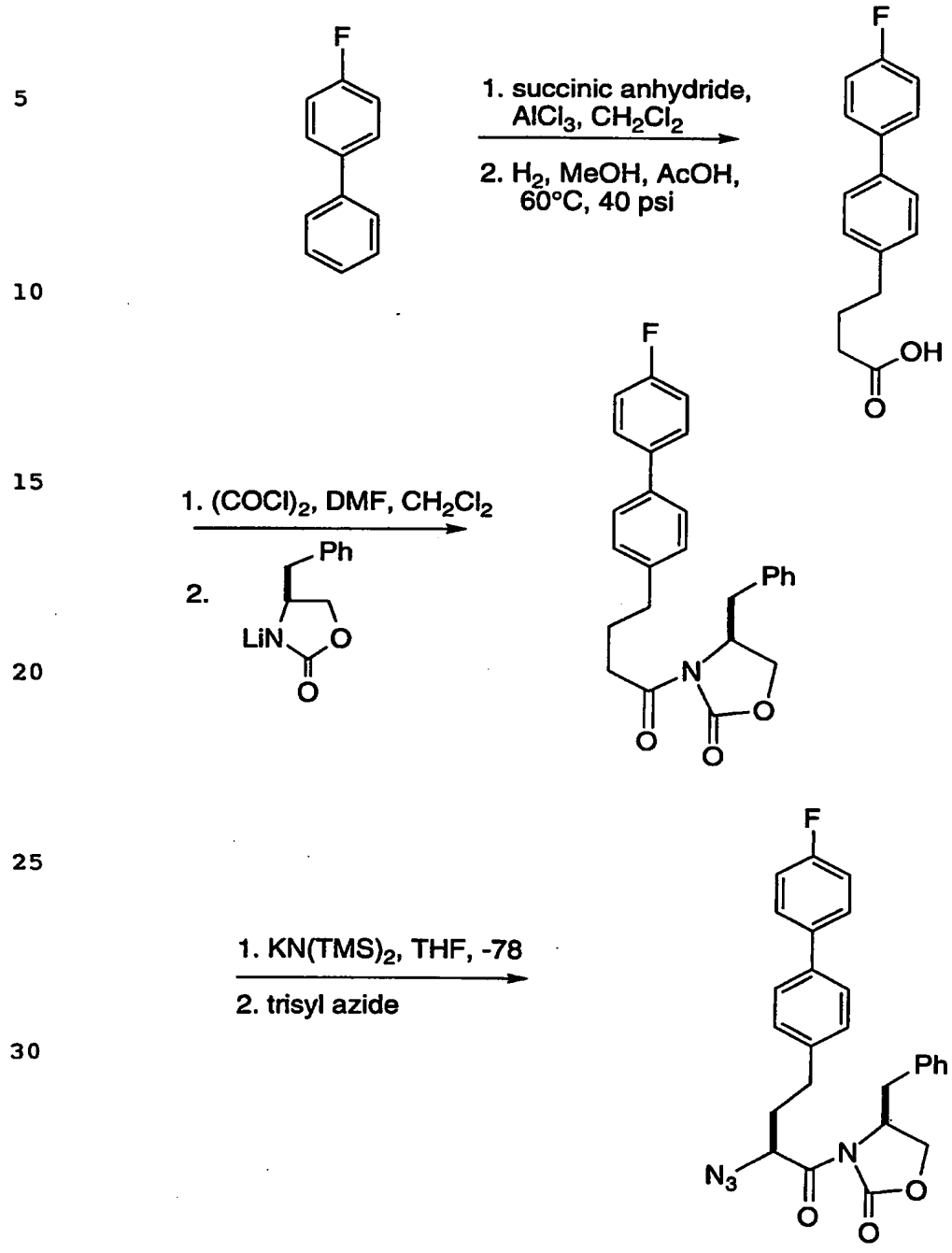
Moreover the invention also encompasses compositions, treatment, and method for co-administration of a compound of Formula I with a PMN elastase inhibitor such as those described in EP 0 337 549 which published on October 18, 1989, which is hereby incorporated by reference.

As may be appreciated by those of skill in the metalloendoproteinase art, it may be important to treat a patient with a matrix metalloendoproteinase mediated disease with an inhibitor that is specific for one or more matrix metalloendoproteinase (such as stromelysin, or collagenase or gelatinase). For example, it may be advantageous to treat a pateint with a compound that is a potent

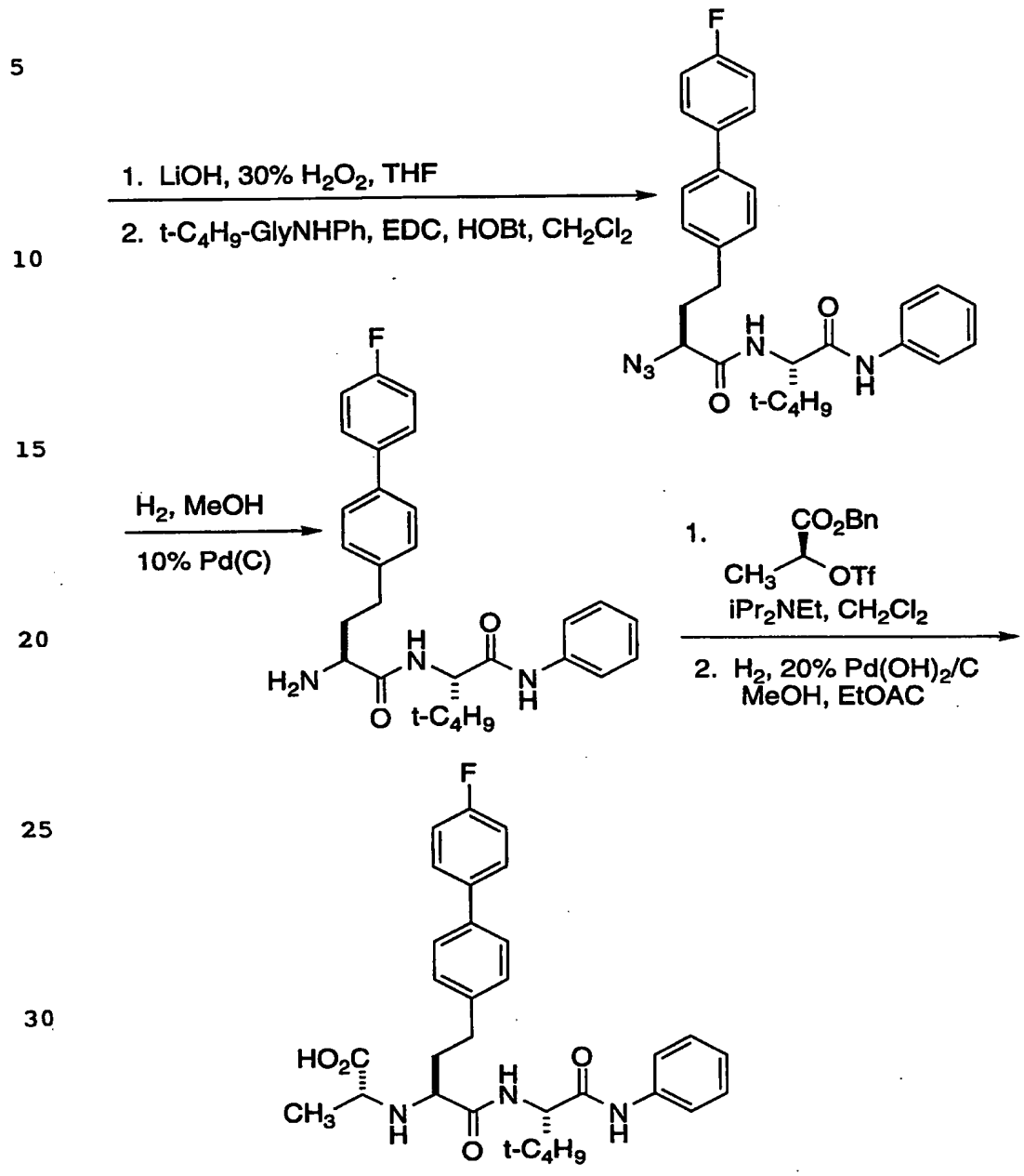
inhibitor of stromelysin but is a weak inhibitor of collagenase, or vice versa.

Compounds of the instant invention are conveniently prepared using the procedures described generally below and more explicitly described in the Example section thereafter.

SCHEME 1


F
1. succinic anhydride, AlCl3, CH2Cl2
2. H2, MeOH, AcOH, 60°C, 40 psi
OH
O
1. (COCl)2, DMF, CH2Cl2
2.
Ph
LiN
O
O
F
Ph
N
O
O
O
1. KN(TMS)2, THF, -78
2. trisyl azide
F
Ph
N3
N
O
O
O

SCHEME 1 (CONT'D.)



The inhibitors described in Scheme 1 can be prepared as follows: A biaryl derivative is acylated with succinic anhydride in the presence of a Lewis acid. The resulting biaryl ketone is reduced by catalytic hydrogenation to afford a biarylalkyl carboxylic acid. ~~An~~ This arylalkyl carboxylic acid is first converted to its corresponding acid chloride using oxalyl chloride and this is used to acylate lithio-4-benzyl-2-oxazolidinone. The derived imide is reacted with strong base, in this case potassium hexamethyl disilazide, and subsequently treated with triisopropylbenzenesulfonylazide (trisyl azide) to from the α-azido imide. The chiral auxiliary is then remove with lithium hydroperoxide and the resulting acid azide coupled to an amine. The azide is subsequently reduced to the amine by catalytic hydrogenation. The amine is reacted with benzyl lactate O-triflate in the presence of N,N-diisopropylethylamine to form the benzyl ester of an N-carboxyalkyl derivative. Removal of the benzyl ester by catalytic hydrogenation affords the desired inhibitors.

Compounds of the present invention have inhibitory activities with respect to metalloendoproteinases such as stromelysin, collagenase and gelatinase. The capacity to inhibit the hydrolysis of peptidyl substrates by these matrix metalloproteinases may be demonstrated in assays in which the extent of enzymatic cleavage of a peptidyl substrate is determined with varying concentrations of inhibitor by methodology as detailed in the following literature reference: K.T. Chapman, I.E. Kopka, P.L. Durette, C. K. Esser, T.J. Lanza, M. Izquierdo-Martin, L. Niedzwiecki, B. Chang, R.K. Harrison, D.W. Kuo, T.-Y. Lin, R.L. Stein, W.K. Hagmann, J. Med. Chem. 36, 4293-4301 (1993).

This invention also relates to a method of treatment for patients (including man and/or mammalian animals raised in the dairy, meat, or fur industries or as pets) suffering from disorders or diseases which can be attributed to stromelysin as previously described, and more specifically, a method of treatment involving the administration of the matrix metalloendoproteinase inhibitors of Formula (I) as the active constituents.

Accordingly, the compounds of Formula (I) can be used among other things in the treatment of osteoarthritis and rheumatoid arthritis, and in diseases and indications resulting from the over-expression of these matrix metalloendoproteinases such as found in certain metastatic tumor cell lines.

For the treatment of rheumatoid arthritis, osteoarthritis, and in diseases and indications resulting from the over-expression of matrix metalloendoproteinases such as found in certain metastatic tumor cell lines or other diseases mediated by the matrix metalloendo-proteinases, the compounds of Formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or

acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example, polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example, ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example, gum acacia or gum tragacanth, naturally-occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also

be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of Formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of Formula (I) are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.05 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 2.5 mg to about 7 gms. per patient per day). For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 0.5 mg to about 3.5 gms per patient per day).

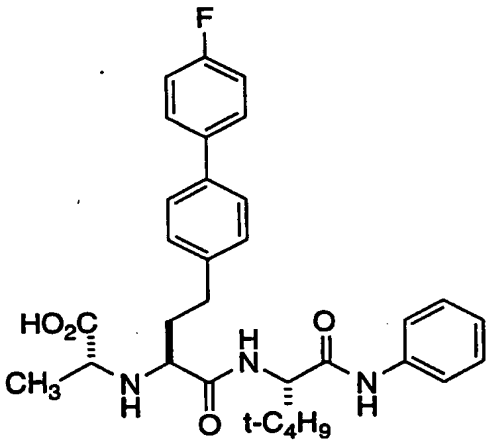
The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 gm of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

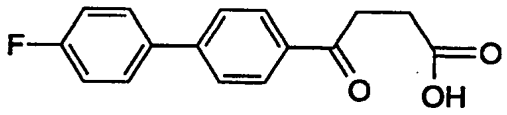
The following Examples are intended to illustrate the preparation of compounds of Formula I, and as such are not intended to limit the invention as set forth in the claims appended, thereto.

EXAMPLE 1

N-[1(R)-Carboxyethyl]-α-(S)-2-(4-fluorobiphenyl)-glycyl(S)-2-(tert-butyl)glycine, N-Phenyl Amide

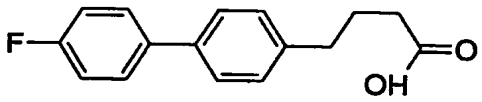


Step 1: 4-(4-Fluorobiphenyl)-4-oxo-butanoic acid



A 500-mL three-neck round-bottom flask equipped with a mechanical stirrer, thermometer, and reflux condenser was charged with methylene chloride (125 mL). 4-Fluorobiphenyl (20.0 g, 0.116 mol) was added followed by succinic anhydride (11.6 g, 0.116 mol). The mixture was cooled in an ice-bath and aluminum chloride (30.9 g, 0.232 mol) was added in six portions at 15-minute intervals. The ice-bath was applied as needed to keep the temperature near 15°C. After the last addition, the mixture was stirred for 90 min at room temperature and then for an additional 90 min at gentle reflux (37-39°C). The cooled reaction mixture was poured into a stirred mixture of ice (300 g) and concentrated hydrochloric acid (40 mL). Additional water (500 mL) was added and the resulting solid filtered, washed with water, and dried by suction. Recrystallization from hot acetic acid afforded pure title compound after drying *in vacuo* at 50°C; yield 19.6 g (62%); 400 MHz ^{1}H NMR ($CDCl_3$): δ 2.83 (t, 2H), 3.33 (t, 2H), 7.11-8.07 (m, 8H).

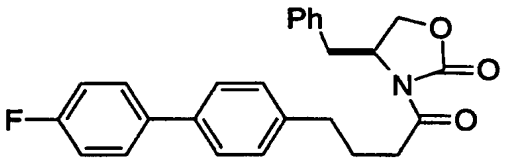
Step 2: 4-(4-Fluorobiphenyl)-butanoic acid



A mixture of 4-(4-fluorobiphenyl)-3-oxo-butanoic acid (19.6 g, 72.0 mmol) in glacial acetic acid (185 mL) and methanol (75 mL) was stirred at 60°C in the presence of 20% palladium hydroxide-on-carbon (1.2 g) under 40 p.s.i. of hydrogen for several hours until thin layer chromatography (20% ethyl acetate in hexane containing 1% acetic acid) indicated complete reduction. The catalyst was removed by filtration through a pad of Celite, and the filtrate was evaporated under

diminished pressure. After several co-evaporations with toluene, the title compound was obtained a white crystalline solid that was dried *in vacuo*; yield 18.3 g (98%); 400 MHz ^{1}H NMR ($CDCl_3$): δ 1.98 (quintet, 2H), 2.40 (t, 2H), 2.69 (t, 2H), 7.08-7.52 (m, 8H).

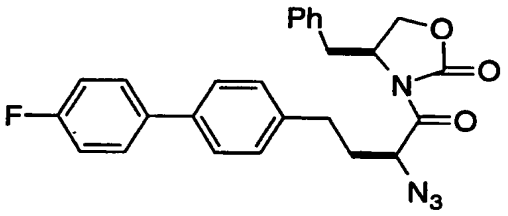
Step 3: 3-(4-(4-Fluorobiphenyl)-butanoyl)-(S)-4-phenylmethyl-2-oxazolidinone



4-(4-Fluorobiphenyl)-butanoic acid (18.3 g, 70.8 mmol) was taken up in methylene chloride (220 mL). N,N-Dimethylformamide (362 µL) was added, and the solution was cooled in an ice bath. Oxalyl chloride (6.85 mL, 78.5 mmol) was added with stirring over 10 min., and the solution was stirred at ice temperature for 30 min and then at room temperature for 2 h. The reaction mixture was evaporated under diminished pressure and dried *in vacuo* for one hour. To a solution of (S)-4-phenylmethyl-2-oxazolidinone (11.4 g, 64.3 mmol) in dry THF (185 mL) cooled to -78°C was added n-butyl lithium (1.6 M in hexanes) (43.4 mL, 69.4 mmol) dropwise with stirring while maintaining the temperature below -60°C. After 15 min., a solution of the acid chloride in THF (30 mL) was added, and the mixture was stirred for 30 min at -78°C. The cooling bath was removed, and stirring was continued for one hour. After quenching with saturated aqueous ammonium chloride (55 mL), ethyl acetate (175 mL) and water (55 mL) were added, and the organic layer separated. The organic layer was washed with 2 N hydrochloric acid, saturated sodium hydrogencarbonate solution, saturated brine solution, dried (sodium sulfate), and evaporated. Crystallization from diethyl ether afforded the desired product. The filtrate was evaporated and subjected to flash silica gel chromatography eluting with 15% ethyl acetate in hexane. A

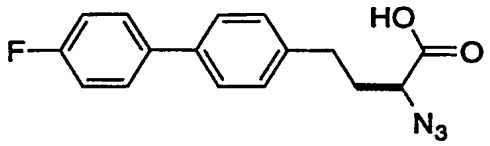
total of 22.5 grams of the title compound was obtained; yield 76%; 400 MHz ^{1}H NMR ($CDCl_3$): δ 2.05 (m, 2H), 2.70-2.78 (m, 3H), 2.98 (m, 2H), 3.28 (dd, 1H), 4.15 (m, 2H), 4.64 (m, 1H), 7.07-7.52 (m, 13H).

Step 4: 3-[(S)-2-Azido-4-(4-fluorobiphenyl)-butanoyl]-(S)-4-phenylmethyl-2-oxazolidinone



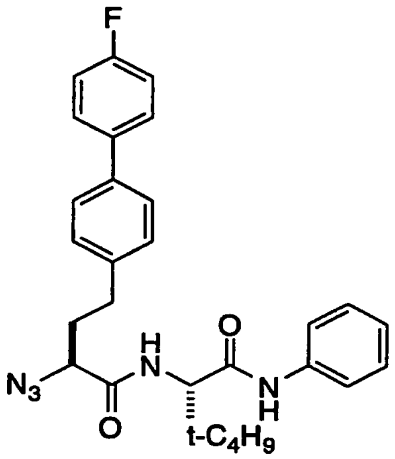
Potassium hexamethyldisilazide (KHMDS) (0.5 M solution in toluene) (6.85 mL, 3.43 mmol) was added to a solution of 3-(4-(4-fluorobiphenyl)-butanoyl)-(S)-4-phenylmethyl-2-oxazolidinone (1.30 g, 3.11 mmol) in dry THF (13 mL) dropwise with stirring at -78°C under a nitrogen atmosphere. The reaction mixture was stirred for 30 min at -78°C, and a solution of trisyl azide (1.20 g, 3.88 mmol) in THF (5 mL) was added dropwise with stirring. The mixture was stirred at -78°C for 10 min. and then quenched with glacial acetic acid (0.82 mL, 14.3 mmol). The cooling bath was removed, and the mixture was stirred overnight at room temperature. It was then concentrated and partitioned between ethyl acetate and water. The organic layer was washed with saturated brine solution, dried (sodium sulfate), and evaporated. The product was purified by flash silica gel chromatography eluting with 10% ethyl acetate in hexane; yield 1.1 g (77%): 400 MHz ^{1}H NMR ($CDCl_3$): δ 2.12 (m, 1H), 2.20 (m, 1H), 3.30 (dd, 1H), 4.16 (m, 2H), 4.57 (m, 1H), 5.00 (dd, 1H).

Step 5: (S)-2-Azido-4-(4-fluorobiphenyl)-butanoic acid



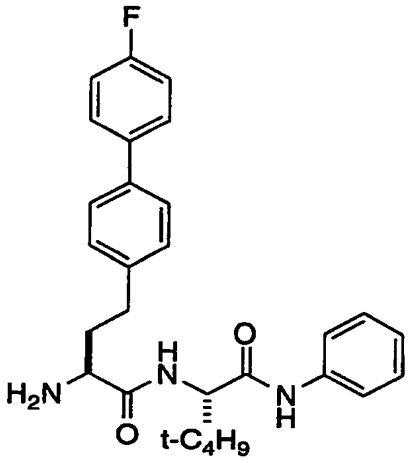
To a solution of 3-[(S)-2-azido-4-(4-fluorobiphenyl)-butanoyl]-(S)-4-phenylmethyl-2-oxazolidinone (1.1 g, 2.40 mmol) in THF (37 mL) and water (11.6 mL) were added 30% hydrogen peroxide (1.34 mL) and lithium hydroxide monohydrate (112 mg, 2.67 mmol). The reaction mixture was stirred overnight at room temperature. The mixture was cooled in an ice bath, and a solution of sodium sulfite (1.86 g) in water (15 mL) followed by saturated sodium hydrogencarbonate solution (15 mL). After removal of the THF by evaporation under diminished pressure, the residue was partitioned between ethyl acetate (75 mL) and 2 N hydrochloric acid (25 mL). The organic layer was washed with saturated brine solution, dried (sodium sulfate), and evaporated. The product was purified by flash silica gel chromatography (packed as a slurry in 20% ethyl acetate in hexane) eluting initially with 20% ethyl acetate in hexane followed by 25% ethyl acetate in hexane containing 1% acetic acid. The title compound was obtained as a white crystalline solid; yield 510 mg (71%); 400 MHz ^1H NMR ($CDCl_3$): δ 2.10 (m, 1H), 2.20 (m, 1H), 2.40 (m, 2H), 4.90 (dd, 1H), 7.07-7.50 (m, 8H).

Step 6: (S)-2-Azido-4-(4-fluorobiphenyl)-butanoyl-(S)-2-(tert-butyl)-glycine, N-phenyl amide



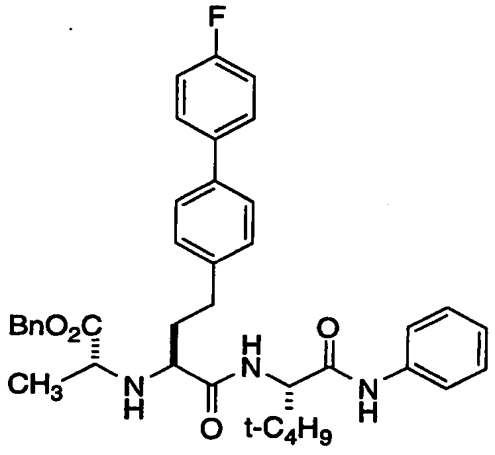
To a solution of (S)-2-azido-4-(4-fluorobiphenyl)-butanoic acid (506 mg, 1.69 mmol) in methylene chloride (10 mL) were added N-hydroxybenzotriazole (342 mg, 2.53 mmol) and (S)-2-(tert-butyl)-glycine N-phenyl amide (366 mg, 1.77 mmol). The reaction mixture was cooled in an ice-bath, and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (389 mg, 2.03 mmol) was added. The reaction mixture was stirred overnight at room temperature, diluted with methylene chloride, washed with water, 2 N hydrochloric acid, saturated sodium hydrogencarbonate solution, saturated brine solution, dried (sodium sulfate), and evaporated. The product was purified by flash silica gel chromatography eluting with 20% ethyl acetate in hexane; yield 610 mg (74%); 400 MHz ^{1}H NMR ($CDCl_3$): δ 1.10 (s, 9H), 2.19 (m, 1H), 2.28 (m, 1H), 2.78 (m, 2H), 4.00 (dd, 1H), 4.46 (d, 1H), 7.08-7.51 (m, 13H), 7.89 (s, 1H).

Step 7: (S)-2-Amino-4-(4-fluorobiphenyl)-butanoyl-(S)-2-(tert-butyl)-glycine, N-phenyl amide



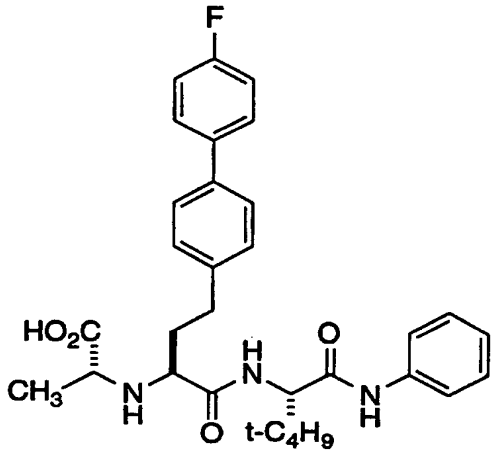
A solution of (S)-2-azido-4-(4-fluorobiphenyl)-butanoyl-(S)-2-(tert-butyl)-glycine N-phenyl amide (308 mg, 0.632 mmol) in methanol (10 mL) was stirred in the presence of 10% palladium-on-charcoal (55 mg) under an atmosphere of hydrogen for 5 hours. The catalyst was removed by filtration through a pad of Celite, and the filtrate was evaporated. The product was purified by flash silica gel chromatography eluting with 2% methanol in methylene chloride; yield 220 mg (75.5%).

Step 8: N-[1(R)-(Benzyloxycarbonyl)ethyl]-α-(S)-2-(4-fluoro-biphenyl)-glycyl-(S)-2-(tert-butyl)glycine, N-phenyl amide



To a solution of benzyl (S)-lactate (86 mg, 0.477 mmol) in dry methylene chloride (3.5 mL) cooled to 0°C was added trifluoromethanesulfonic anhydride (86 µL, 0.511 mmol) with stirring under an inert atmosphere. After 5 min. at 0°C, 2,6-lutidine (62.4 µL, 0.536 mmol) was added in one portion. After stirring for 10 min. at 0°C, N,N-diisopropylethylamine (92 µL, 0.528 mmol) was added followed immediately by a solution of (S)-2-amino-4-(4-fluorobiphenyl)-butanoyl-(S)-2-(tert-butyl)-glycine N-phenyl amide (220 mg, 0.477 mmol) in methylene chloride (2 mL). The cooling bath was removed, and the mixture was stirred overnight at room temperature. The mixture was diluted with methylene chloride which was successively washed with water, saturated sodium hydrogencarbonate solution, saturated brine solution, dried (sodium sulfate), and evaporated. Purification was achieved by means of flash silica gel chromatography eluting with 20% ethyl acetate in hexane. The product was obtained as a white crystalline solid; yield 70.4 mg (24%); mass spectrum: m/z 624 (M + 1); 400 MHz ^{1}H NMR (CD_3OD): δ 1.08 (s, 9H), 1.31 (d, 3H), 1.92 (m, 1H), 2.02 (m, 1H), 2.73 (m, 2H), 3.48 (q, 1H), 4.40 (s, 1H), 5.12 (m, 2H), 7.07-7.58 (m, 18H).

Step 9: N-[1(R)-(Carboxyethyl]-α-(S)-2-(4-fluorobiphenyl)-glycyl-(S)-2-(tert-butyl)glycine, N-phenyl amide



A solution of N-[1(R)-(benzyloxycarbonyl)ethyl]-α-(S)-2-(4-fluorobiphenyl)-glycyl-(S)-2-(tert-butyl)glycine, N-phenyl amide (70 mg, 0.112 mmol) in methanol (4 mL) was stirred in the presence of 20% palladium hydroxide-on-carbon (20 mg) under an atmosphere of hydrogen for 2 hours. The catalyst was removed by filtration through an Anotop 25 disposable syringe filter (0.2 μm). The filtrate was evaporated to give the title compound as an amorphous solid; yield 58.2 mg (97%); mass spectrum: m/z 534 (M + 1); 400 MHz ^{1}H NMR (CD_3OD): 1.12 (s, 9H), 1.51 (d, 3H), 2.18 (m, 2H), 2.70 (m, 2H), 3.62 (q, 1H), 4.18 (dd, 1H), 4.52 (s, 1H), 7.08-7.57 (m, 13H).

EXAMPLE 2

ENZYME INHIBITON ASSAYS

Inhibition of Human Fibroblast Stromelysin.

Activation: Human recombinant stromelysin was purchased from Celltech (Slough, U.K.) as a proenzyme of 55kD in a buffer consisting of 20 mM Tris, 10 mM $CaCl_2$, 0.05% Brij-35, and 0.2% NaN_3, pH=7.5. Briefly, to 1.0 mL of a 2.2 μM solution of prostromelysin was added 20 μL of a 1.0 μM solution of trypsin in assay buffer (20 mM HEPES, 10mM $CaCl_2$, 0.05% Brij-35, pH=7.5, [trypsin]final = 20 nM. The solution was incubated at 37°C for 30 minutes. The reaction was quenched by addition of a 50 fold molar excess of soybean trypsin inhibitor bound to agarose (Sigma), and the solution centrifuged to remove the trypsin:inhibitor complex.

K_i Determinations: Stock solutions of inhibitors were prepared by dissolving the compounds in DMSO. The inhibitors were further diluted in assay buffer to eight different concentrations encompassing the approximate K_i, and covering a 200 fold range. To 50 μL of each of the inhibitor solutions was added 25 μL of an 8 nM solution of trypsin-activated stromelysin, [DMSO] = 1.8%. The solution was allowed to incubate for 4 h to reach equilibrium. To this solution was added 60 μL of a 12.8 μM solution of the substrate Arg-Pro-Lys-Pro-Leu-Ala-Phe-Trp-NH_2, and the reaction was allowed to proceed for 18 h. In the reaction [S] = 5.7 μM and [E] = 1.5 nM. The reaction was quenched by addition of 50 μL of 0.15M phosphoric acid, and 100 μL of the reaction mixture was injected onto the HPLC. Since the reactions were run under first order conditions, ([S]<<K_m, K_m = 0.5 mM), the pseudo first order rate constant, k_{obs}, was determined for each of the inhibitor concentrations from the peak area corresponding to unreacted substrate in the inhibited sample, and the peak area for substrate at time = 0:

$$\ln \frac{area_{inhib}}{area_{t=0}} = -k_{obs}t$$

Values of K_i were determined from the ratio of the rate constants for inhibited and control sample (no inhibitor) plotted as a function of the inhibitor concentration, and fit to the following equation:

$$\frac{k_{inhib}}{k_{control}} = \frac{1}{1 + [I]/K_i}$$

Inhibition of Human Fibroblast Collagenase

Activation. Human fibroblast collagenase was purchased from Celltech (Slough, U.K.). The material was received as a proenzyme of 54 kD at a concentration of 1.2 μM in a buffer consisting of 20 mM Tris, 5 mM $CaCl_2$, 0.15 M NaCl, and 0.01% NaN_3. The material was activated with trypsin using the same procedure as for stromelysin, with the addition that the activation buffer contained 40 nM prostromelysin.

K_i Determinations. Stock solutions of inhibitors were prepared by dissolving the material in DMSO The inhibitors were further diluted in assay buffer to eight different concentrations encompassing the approximate K_i and covering a 200 fold range. Final DMSO concentration was 2.8%. To 50 uL of the inhibitor solutions was added 25 uL of a 108 nM solution of trypsin activated collagenase. The solution was allowed to incubated for 4 h to reach equilibrium. To this solution was added 60 uL of a 56 μM solution of the substrate DNP-Pro-Leu-Gly-Leu-Trp-Ala-dArg-NH_2, and the reaction was allowed to proceed for 18 h. In the incubation mixture [S] = 25 μM, [E]= 20 nM. The reaction was quenched by addition of 50 uL of 0.15 M phosphoric acid. The reaction mixture was injected onto the HPLC. The calculation of K_i was the same as for stromelysin.

Inhibition of Human Gelatinase A.

Activation: Human 72kD gelatinase was purchased from Celltech (Slough, U.K.) as a proenzyme at a concentration of 1.5 μM in a buffer consisting of 20 mM Tris, 5mM $CaCl_2$ 150 mM NaCl, 0.01% brij, 0.02% NaN_3, pH = 7.5 . The proenzyme was activated by incubation of

500 µL proenzyme with 50 µL of a 11 mM solution aminophenyl mercuric acetate in NaOH (pH=11) at 25°C for 120 min.

K_i Determinations. Determination of K_i values for gelatinase A were identical to that of collagenase and stromelysin with the exception that incubation of the enzyme-inhibitor mixture with the substrate was performed for only 2 h. [S] = 25 µM, [E]= 20 nM.

Employing the assays described herein, the compound described in Example 1 inhibited the matrix metalloproteinases as follows:
stromelysin K_i = 22 nM;
collagenase K_i = 3.1 µM;
gelatinase-A K_i = 37 nM.

EXAMPLE 3

IN VIVO EVALUATION OF INHIBITORS

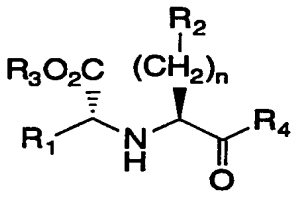
Recombinant human stromelysin (rhSLN) was purchased from Celltech, Ltd, UK, and purified in our laboratories. It was standardized *in vitro* by activating with trypsin and titrations of its proteolytic activity for [^{3}H]l-transferrin. After time and dose studies, 100 µg of activated rhSLN dissolved in 0.5 ml of stromelysin buffer (25 mM Tris-HCl, 0.7 M NaCl, 10 mM $CaCl_2$, 0.05% Brij, 0.02% NaN_3, pH 7.5) was injected intraarticularly into the synovial cavity of a stifle joint of 8 - 10 wk female New Zealand White rabbits (Hazelton Farms, Denver, PA) that had been anesthetized with a mixture (3:2, v/v) of ketamine HCl (100 mg/kg; Ketaset®, Aveco Co, Inc, Ft Dodge IN) and xylazine (20 mg/kg; Rompum®, Mobay Corp, Shawnee KA). As a control, the contralateral stifle joint was injected with 0.5 ml of stromelysin buffer. 1 hr after the intraarticular injection of activated rhSLN, the animals were euthanized with an overdose of sodium pentobarbital and each joint was lavaged twice with 0.5 ml of PBS. The total mass of proteoglycans lavaged from the stifle joint of the rhSLN-injected animal minus the mass of proteoglycans lavaged from the contralateral control

joint (net activated rhSLN-induced increase in proteoglycans in synovial fluid) is a quantitative assessment of the in vivo potency of activated rhSLN.

Investigational compounds were dissolved in 100% DMSO and then diluted to 2% DMSO, 2% Cremaphore® (polyoxyethylene glycerol triricinoleate, BASF Corp, Parsippany NJ), 96% 50 mM phosphate-buffered saline, pH 7.0. The compounds were either injected intravenously or per orally at various times prior to the intraarticular injection of activated rhSLN. The capacity of the investigational compounds to reduce the net amount of proteoglycans in the synovial cavity is a quantitative measurement of their potency and is expressed as % inhibition or ED_{50}.

WHAT IS CLAIMED IS:

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof wherein:

n = 2-3;

R_1 is hydrogen or mono- or di-substituted C_{1-6}alkyl or a mono- or di-substituted C_{2-6}alkenyl wherein the substituents are independently selected from the group consisting of:

(a) hydrogen,
(b) carboxy,
(c) aminocarbonyl,
(d) C_{1-6}alkoxy,
(e) C_{1-6}alkylthio,
(f) C_{1-6}alkylsulfinyl,
(g) C_{1-6}alkylsulfonyl,
(h) C_{1-6}alkylcarbonyl,
(i) aryl group selected from the group consisting of:
  (1) phenyl,
  (2) naphthyl,
  (3) pyridyl,
  (4) pyrryl,
  (5) furyl,
  (6) thienyl,

(7) isothiazolyl,
(8) imidazolyl,
(9) benzimidazolyl,
(10) tetrazolyl,
(11) pyrazinyl,
(12) pyrimidyl,
(13) quinolyl,
(14) isoquinolyl,
(15) benzofuryl,
(16) isobenzofuryl,
(17) benzothienyl,
(18) pyrazolyl,
(19) indolyl,
(20) isoindolyl,
(21) purinyl,
(22) carboxazolyl,
(23) isoxazolyl,
(24) thiazolyl,
(25) oxazolyl,
(26) benzthiazolyl, and
(27) benzoxazolyl,

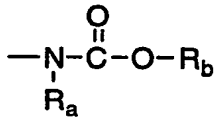
optionally mono- or di-substituted with substitutents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, halo, hydroxy, amino, C_{1-6}alkylamino, aminoC_{1-6}alkyl, carboxyl, carboxylC_{1-6}alkyl, or C_{1-6}alkylcarbonyl,;

(j) aryloxy wherein the aryl groups are defined above in item (i);
(k) aroyl wherein the aryl groups are defined above in item (i);
(l) amino or mono- or di-substituted amino wherein the substituents are independently selected from C_{1-6}alkyl and aryl as defined above in item (i);
(m) arylthio wherein the aryl groups are defined above in item (i);

(n) arylsulfinyl wherein the aryl groups are defined above in item (i);

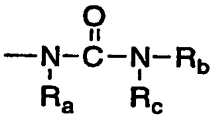
(o) arylsulfonyl wherein the aryl groups are defined above in item (i);

(p)



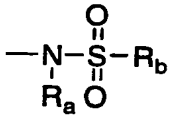
wherein R_a and R_b are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its substituents are as defined in (i) above, or
wherein Ra and Rb are joined together with the nitrogen and oxygen atoms to which they are attached to form a saturated or unsaturated cyclic-urethane, or a saturated or unsaturated benzofused cyclic-urethane, wherein the urethane ring contains 5, 6, 7, or 8 atoms, said ring containing two heteroatoms N and O;

(q)



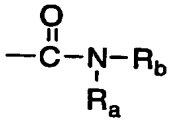
wherein R_a R_b, and R_c are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its substituents areas defined in (i) above, or
wherein Ra and Rb are joined together with the nitrogen atoms to which they are attached to form a saturated or unsaturated cyclic-urea or saturated or unsaturated benzofused cyclic-urea, said urea ring containing 5, 6, 7, or 8 atoms and two heteroatoms which are nitrogens;

(r)



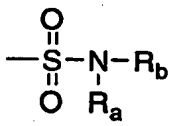
wherein R_a and R_b are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its substituents areas defined in (i) above, or
wherein Ra and Rb are joined together with the nitrogen and sulfur atoms to which they are attached, to form a saturated or unsaturated cyclic-sulfonamide or saturated or unsaturated benzofused cyclic-sulfonamide ring, said sulfonamide ring containing 5, 6, 7, or 8 atoms and two heteroatoms which are N and S;

(s)



wherein R_a and R_b are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its substituents areas defined in (i) above, or
wherein Ra and Rb are joined together with the nitrogen atom to which they are attached, to form a saturated or unsaturated heterocycle or staurated or unsaturated benzofused heterocycle ring, said ring containing 5, 6, 7, or 8 atoms and a heteroatom which is nitrogen;

(t)



wherein R_a and R_b are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its substituents areas defined in (i) above, or
wherein Ra and Rb are joined together with the nitrogen atom to which they are attached, to form a saturated or unsaturated heterocycle or saturated or unsaturated benzofused heterocycle ring, said ring containing 5, 6, 7, or 8 atoms including a heteroatom which is nitrogen;

R_2 is biaryl wherein the aryl group is selected from the group consisting of:

(1) phenyl,
(2) naphthyl,
(3) pyridyl,
(4) pyrryl,
(5) furyl,
(6) thienyl,
(7) isothiazolyl,
(8) imidazolyl,
(9) benzimidazolyl,
(10) tetrazolyl,
(11) pyrazinyl,
(12) pyrimidyl,
(13) quinolyl,
(14) isoquinolyl,
(15) benzofuryl,
(16) isobenzofuryl,
(17) benzothienyl,
(18) pyrazolyl,
(19) indolyl,

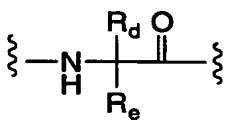
(20) isoindolyl,
(21) purinyl,
(22) carboxazolyl,
(23) isoxazolyl,
(24) thiazolyl,
(25) oxazolyl,
(26) benzthiazolyl, and
(27) benzoxazolyl,

optionally mono or di-substituted with substitutents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo, haloalkyl, hydroxy, amino, C_{1-6}alkylamino, aminoC_{1-6}alkyl, aminosulfonyl, aminocarbonyl, ureido, sulfonylureido, C_{1-6}alkoxycarbonyl, carboxyl, carboxylC_{1-6}alkyl, and C_{1-6}alkylcarbonyl;

R_3 is

(a) H,
(b) Z, where Z is a pharmaceutically acceptable counterion,
(c) C_{1-10}alkyl,
(d) aryl or aryl C_{1-3}alkyl, wherein the aryl group is selected from the group consisting of
  (1) phenyl, and
  (2) substituted phenyl, wherein the substitutent is carboxy, carboxyC_{1-3}alkyl, aminocarbonyl, C_{1-6}alkylaminocarbonyl;

R_4 is X-R_5 wherein X is a single bond or an amino acid of formula **II**

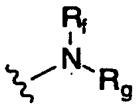


II

wherein R_d and R_e are individually selected from:

(a) hydrogen,
(b) C_{1-6}alkyl,
(c) mercapto C_{1-6}alkyl,
(d) hydroxy C_{1-6}alkyl,
(e) carboxy C_{1-6}alkyl,
(f) amino substituted C_{1-6}alkyl
(g) aminocarbonyl C_{1-6}alkyl,
(h) mono- or di-C_{1-6}alkyl amino C_{1-6}alkyl,
(i) guanidino C_{1-6}alkyl,
(j) substituted phenyl C_{1-6}alkyl, wherein the substitutent is hydrogen,hydroxy, carboxy, C_{1-4} alkyl, or C_{1-4}alkyloxy,
(k) substituted indolyl C_{1-6}alkyl, wherein the substitutent is hydrogen, hydroxy, carboxy, C_{1-4} alkyl, or C_{1-4}alkyloxy,
(l) substituted imidazolyl C_{2-6}alkyl wherein the substitutent is hydrogen, hydroxy, carboxy, C_{1-4} alkyl, or C_{1-4}alkyloxy,
(m) substituted pyridyl C_{1-6}alkyl wherein the substitutent is hydrogen, hydroxy, carboxy, C_{1-4} alkyl, or C_{1-4}alkyloxy,
(n) substituted pyridylamino C_{1-6}alkyl wherein the substitutent is hydrogen, hydroxy, carboxy, C_{1-4} alkyl, or C_{1-4}alkyloxy,
(o) substituted pyrimidinyl C_{1-6}alkyl wherein the substitutent is hydrogen, hydroxy, carboxy, C_{1-4} alkyl, or C_{1-4}alkyloxy,

R_5 is



wherein R_f and R_g are each individually selected from the group consisting of:

(a) H,
(b) substituted C_{1-10}alkyl wherein the substituents are independently selected from hydrogen, C_{1-6}alkyloxy,

hydroxy, halo, amino, C_{1-6}alkylamino, carboxyl, and C_{1-6}alkylcarbonyl;

(c) Aryl or arylC_{1-6}alkyl, wherein the aryl group is selected from the group consisting of

(1) phenyl,
(2) naphthyl,
(3) pyridyl,
(4) pyrryl,
(5) furyl,
(6) thienyl,
(7) isothiazolyl,
(8) imidazolyl,
(9) benzimidazolyl,
(10) tetrazolyl,
(11) pyrazinyl,
(12) pyrimidyl,
(13) quinolyl,
(14) isoquinolyl,
(15) benzofuryl,
(16) isobenzofuryl,
(17) benzothienyl,
(18) pyrazolyl,
(19) indolyl,
(20) isoindolyl,
(21) purinyl,
(22) carbazolyl,
(23) isoxazolyl,
(24) benzthiazolyl,
(25) benzoxazolyl,
(26) thiazolyl, and
(27) oxazolyl.

optionally mono or di-substituted with substitutents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl,

halo, haloalkyl, hydroxy, amino, C_{1-6}alkylamino, aminoC_{1-6}alkyl, aminosulfonyl, aminocarbonyl, ureido, sulfonylureido, C_{1-6}alkoxycarbonyl, carboxyl, carboxylC_{1-6}alkyl, and C_{1-6}alkylcarbonyl;or

(d) R_f and R_g are joined together with the nitrogen atom to which they are attached, to form a heterocycle ring, wherein the heterocycle is selected from the group consisting of

(1) morpholine,
(2) thiomorpholine,
(3) thiomorpholine sulfone,
(4) pyrrolidine,
(5) piperazine,
(6) piperidine,
(7) 3-ketopiperazine, and
(8) 2-ketopiperazine;

optionally mono or di-substituted with substitutents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, halo, hydroxy, amino, C_{1-6}alkylamino, carboxyl, carboxylC_{1-6}alkyl, and C_{1-6}alkylcarbonyl.

2. A compound according to Claim 1 wherein

n = 2-3; and

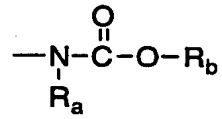
R_1 is hydrogen or mono- or di-substituted C_{1-6}alkyl wherein the substituents are independently selected from the group consisting of:

(a) hydrogen,
(b) C_{1-6}alkoxy,
(c) aryl group selected from the group consisting of:
(1) phenyl,
(2) naphthyl,
(3) pyridyl,
(4) pyrryl,
(5) furyl,
(6) thienyl,

(7) isothiazolyl,
(8) imidazolyl,
(9) benzimidazolyl,
(10) tetrazolyl,
(11) pyrazinyl,
(12) pyrimidyl,
(13) quinolyl,
(14) isoquinolyl,
(15) benzofuryl,
(16) isobenzofuryl,
(17) benzothienyl,
(18) pyrazolyl,
(19) indolyl,
(20) isoindolyl,
(21) purinyl,
(22) carboxazolyl,
(23) isoxazolyl,
(24) thiazolyl,
(25) oxazolyl,
(26) benzthiazolyl, and
(27) benzoxazolyl,

optionally mono- or di-substituted with substitutents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, chloro, fluoro, bromo, hydroxy, amino, C_{1-6}alkylamino, aminoC_{1-6}alkyl, carboxyl, carboxylC_{1-6}alkyl, or C_{1-6}alkylcarbonyl,

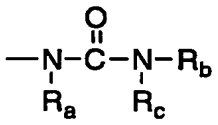
(d)



wherein R_a and R_b are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its optional substituents are as defined in (c) above, or

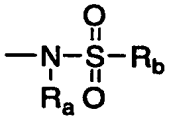
wherein Ra and Rb are joined together with the nitrogen and oxygen atoms to which they are attached to form a saturated or unsaturated cyclic-urethane, or a saturated or unsaturated benzofused cyclic-urethane, wherein the urethane ring contains 5, 6, 7, or 8 atoms, said ring containing two heteroatoms N and O;

(e)



wherein R_a R_b, and R_c are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its optional substituents areas defined in (c) above, or
wherein Ra and Rb are joined together with the nitrogen atoms to which they are attached to form a saturated or unsaturated cyclic-urea or saturated or unsaturated benzofused cyclic-urea, said urea ring containing 5, 6, 7, or 8 atoms and two heteroatoms which are nitrogens;

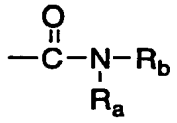
(f)



wherein R_a and R_b are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its optional substituents areas defined in (c) above, or
wherein Ra and Rb are joined together with the nitrogen and sulfur atoms to which they are attached, to form a saturated or unsaturated cyclic-sulfonamide or saturated or unsaturated benzofused cyclic-sulfonamide ring, said sulfonamide ring

containing 5, 6, 7, or 8 atoms and two heteroatoms which are N and S;

(g)



wherein R_a and R_b are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its optional substituents areas defined in (c) above, or
wherein Ra and Rb are joined together with the nitrogen atom to which they are attached, to form a saturated or unsaturated heterocycle or staurated or unsaturated benzofused heterocycle ring, said ring containing 5, 6, 7, or 8 atoms and a heteroatom which is nitrogen.

3. A compound according to Claim 2 wherein R_2 is biaryl wherein the aryl group is selected from the group consisting of:

(1) phenyl,
(2) naphthyl,
(3) thienyl,
(4) imidazolyl,
(5) pyrimidyl,
(6) benzofuryl,
(7) pyridyl,
(8) benzothienyl,

optionally mono or di-substituted with substitutents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo, haloalkyl, hydroxy, amino, C_{1-6}alkylamino, aminoC_{1-6}alkyl, aminosulfonyl, aminocarbonyl, ureido, sulfonylureido, C_{1-6}alkoxycarbonyl, carboxyl, carboxylC_{1-6}alkyl, and C_{1-6}alkylcarbonyl.

4. A compound according to Claim 3 wherein

n = 2-3;

R_1 is hydrogen or mono- or di-substituted C_{1-6}alkyl wherein the substituents are independently selected from the group consisting of:

(a) hydrogen,

(b) C_{1-6}alkoxy,

(c) aryl group selected from the group consisting of:

(1) phenyl,

(2) naphthyl,

(3) thienyl,

(4) imidazolyl,

(5) pyrimidyl,

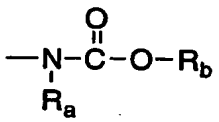
(6) benzofuryl,

(7) pyridyl,

(8) benzothienyl,

optionally mono or di-substituted with substrituents independently selected from C_{1-4}alkyl, C_{1-4}alkyloxy, hydroxy, chloro, fluoro, bromo, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, carboxyl, carboxylC_{1-4}alkyl, and C_{1-4}alkylcarbonyl,

(d)



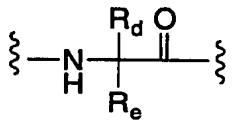
wherein R_a and R_b are each independently hydrogen, C_{1-6} alkyl, optionally substituted aryl wherein aryl and its optional substituents are as defined in (c) above, or

wherein Ra and Rb are joined together with the nitrogen and oxygen atoms to which they are attached to form a saturated or unsaturated cyclic-urethane, or a saturated or unsaturated benzofused cyclic-

urethane, wherein the urethane ring contains 5, 6, 7, or 8 atoms, said ring containing two heteroatoms N and O.

5. A compound according to Claim 4 wherein

R_4 is X-R_5 wherein X is a single bond or an amino acid of formula **II**

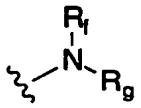


II

wherein R_d and R_e are individually selected from:

(a) hydrogen,
(b) C_{1-4}alkyl,
(c) mercapto C_{1-3}alkyl,
(d) hydroxy C_{1-4}alkyl,
(e) carboxy C_{1-4}alkyl,
(f) amino substituted C_{2-4}alkyl
(g) aminocarbonyl C_{1-4}alkyl,
(h) mono- or di-C_{1-4}alkyl amino C_{2-4}alkyl,
(i) guanidino C_{2-4}alkyl,
(j) substituted phenyl C_{1-4}alkyl, wherein the substitutent is hydrogen,hydroxy, carboxy, C_{1-3} alkyl, or C_{1-3}alkyloxy,
(k) substituted indolyl C_{1-3}alkyl, wherein the substitutent is hydrogen, hydroxy, carboxy, C_{1-3}alkyl, or C_{1-3}alkyloxy,
(l) substituted imidazolyl C_{2-4}alkyl wherein the substitutent is hydrogen, hydroxy, carboxy, C_{1-3} alkyl, or C_{1-3}alkyloxy,

R_5 is



wherein R_f and R_g are each individually selected from the group consisting of:

(a) H,

(b) substituted C_{1-6}alkyl wherein the substituents are independently selected from hydrogen, C_{1-4}alkyloxy, hydroxy, chloro, fluoro, bromo, amino, C_{1-4}alkylamino, carboxyl, and C_{1-4}alkylcarbonyl;

(c) aryl or arylC_{1-6}alkyl, wherein the aryl group is selected from the group consisting of

(1) phenyl,
(2) naphthyl,
(3) pyridyl,
(4) thienyl,
(5) tetrazolyl,
(6) pyrazinyl,
(7) pyrimidyl,
(8) benzofuryl,
(9) benzothienyl,
(10) pyrazolyl,
(11) indolyl,

optionally mono or di-substituted with substitutents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo, haloalkyl, hydroxy, amino, C_{1-6}alkylamino, aminoC_{1-6}alkyl, aminosulfonyl, aminocarbonyl, ureido, sulfonylureido, C_{1-6}alkoxycarbonyl, carboxyl, carboxylC_{1-6}alkyl, and C_{1-6}alkylcarbonyl.

6. A compound according to Claim 5 wherein

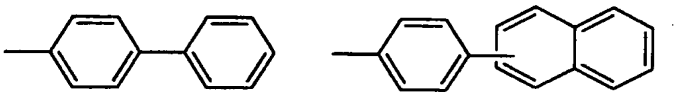
X is an amino acid selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, α-*tert*-butyl-glycine,serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxy-lysine, histidine, arginine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, ornithine, homoserine, or citrulline.

7. A compound according to Claim 5 wherein R3 is

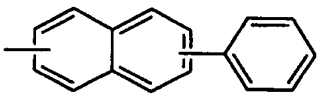
(a) H,
(b) Z, where Z is a pharmaceutically acceptable counterion,
(c) C_{1-4}alkyl,
(d) aryl or aryl C_{1-3}alkyl, wherein the aryl group is selected from the group consisting of
(1) phenyl, and
(2) substituted phenyl, wherein the substitutent is carboxy, carboxyC_{1-3}alkyl, aminocarbonyl.

8. A compound according to Claim 7 wherein

R2 is biaryl selected from the group consisting of



and



optionally mono or di-substituted with substitutents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo, haloalkyl, hydroxy, amino, C_{1-6}alkylamino, aminoC_{1-6}alkyl,

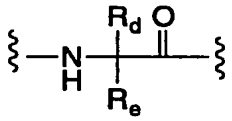
aminosulfonyl, aminocarbonyl, ureido, sulfonylureido, C_{1-6}alkoxycarbonyl, carboxyl, carboxylC_{1-6}alkyl, and C_{1-6}alkylcarbonyl.

9. A compound according to Claim 8 wherein

R4 is X-R5 wherein X is a single bond.

10. A compound according to Claim 8 wherein

R4 is X-R5 wherein X is an amino acid of formula II

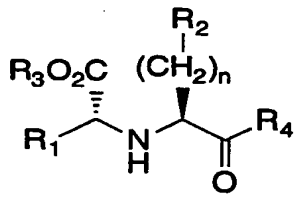


II

wherein R_d and R_e are individually selected from:

(a) hydrogen,
(b) C_{1-3}alkyl,
(c) mercapto C_{1-3}alkyl,
(d) hydroxy C_{1-6}alkyl,
(e) carboxy C_{1-3}alkyl,
(f) amino substituted C_{2-3}alkyl
(g) aminocarbonyl C_{1-3}alkyl,
(h) mono- or di-C_{1-3}alkyl amino C_{2-3}alkyl,
(i) guanidino C_{2-6}alkyl,
(j) substituted phenyl C_{1-3}alkyl, wherein the substitutent is hydrogen,hydroxy, carboxy, C_{1-3} alkyl, or C_{1-3}alkyloxy,
(k) substituted indolyl C_{1-6}alkyl, wherein the substitutent is hydrogen, hydroxy, carboxy, C_{1-3} alkyl, or C_{1-3}alkyloxy,
(l) substituted imidazolyl C_{2-3}alkyl wherein the substitutent is hydrogen, hydroxy, carboxy, C_{1-3} alkyl, or C_{1-3}alkyloxy.

11. A compound of Formula I according to Claim 10



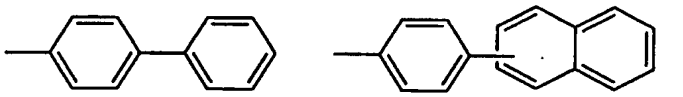
I

wherein
n = 2;

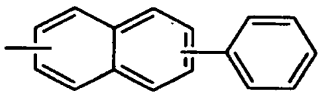
R_1 is hydrogen or mono- or di-substituted C_{1-6}alkyl wherein the substituents are independently selected from the group consisting of:

(a) hydrogen, and
(b) C_{1-6}alkoxy;

R_2 is biaryl selected from the group consisting of



and



optionally mono or di-substituted with substitutents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo, haloalkyl, hydroxy, amino, C_{1-6}alkylamino, aminoC_{1-6}alkyl,

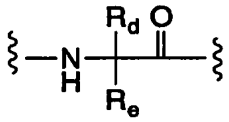
aminosulfonyl, aminocarbonyl, ureido, sulfonylureido, C_{1-6}alkoxycarbonyl, carboxyl, carboxylC_{1-6}alkyl, and C_{1-6}alkylcarbonyl;

R_3 is

(a) H, or

(b) Z, where Z is a pharmaceutically acceptable counterion;

R_4 is X-R_5 wherein X is an amino acid of formula **II**



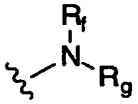
II

wherein R_d and R_e are individually selected from:

(a) hydrogen, or

(b) C_{1-4}alkyl,

R_5 is



wherein R_f is

(a) H, or

(b) substituted C_{1-2}alkyl wherein the substituents are independently selected from hydrogen, C_{1-2}alkyloxy, hydroxy, chloro, fluoro, bromo, amino, C_{1-2}alkylamino, carboxyl, and C_{1-2}alkylcarbonyl, and

R_g is selected from the group consisting of:

(a) substituted C_{1-6}alkyl wherein the substituents are independently selected from hydrogen, C_{1-4}alkyloxy,

hydroxy, chloro, fluoro, bromo, amino, C_{1-4}alkylamino, carboxyl, and C_{1-4}alkylcarbonyl;

(b) aryl or arylC_{1-6}alkyl, wherein the aryl group is selected from the group consisting of

(1) phenyl,
(2) pyridyl,
(3) thienyl,
(4) tetrazolyl,
(5) pyrazinyl,
(6) pyrazolyl,

optionally mono or di-substituted with substitutents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, halo, haloC_{1-6}alkyl, hydroxy, amino, C_{1-6}alkylamino, aminoC_{1-6}alkyl, aminosulfonyl, carboxyl, carboxylC_{1-6}alkyl, and C_{1-6}alkylcarbonyl.

12. A compound which is N-[1(R)-Carboxyethyl]-α-(S)-2-(4-fluorobiphenyl)-glycyl-(S)-2-(tert-butyl)glycine, N-Phenyl Amide.

13. A pharmaceutical composition for treating a matrix metalloendoproteinase-mediated disease comprising a pharmaceutical carrier and a non-toxic effective amount of the compound of Claim 1.

14. A method for inhibiting the lytic activity of metalloendoproteinases comprising administering to a subject suffering from matrix metalloendoproteinase mediated disease, and inhibitory amount of the compound of Claim 1.

15. A method according to Claim 12 in which the metalloendoproteinase is stromelysin.

16. A method according to Claim 12 in which the metalloendoproteinase is gelatinase.

17. A method for inhibiting the activity of stromelysin comprising administering to a subject suffering from a stromelysin mediated disease, a therapeutic amount of the compound of Claim 1.

18. A method according to Claim 16 wherein the stromelysin inhibitor is administered in an amount of from about 0.01 to 50 mg of the compound per kilogram body weight.

19. A method of treating matrix metalloendoproteinase-mediated disease comprising the administration to a subject in need of such a therapeutically effective amount of a compound Claim 1.

20. A method of treating matrix metalloendoproteinase-mediated disease comprising the administration to a subject in need of such a therapeutically effective amount of a compound of Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/04964

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 38/00, 38/02, C07K 5/00, C07K 7/00
US CL : 530/323

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/323, 331

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE- FILE REGISTRY, BEILSTEIN, HCAOLD, HCAPLUS, CA, USPATFULL (structure search)

search terms: C29H32FN303,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A, 92/21360, (SAHOO ET AL) 10 December 1992, see entire document.	1-20
Y	US, A, 5,270,326, (GALADY ET AL) 14 December 1993, columns 2-5.	1-20
Y	US, A, 4,771,037 (ROBERTS ET AL) 13 SEPTEMBER 1988, see entire document.	1-13
Y	US, A, 4,511,504 (MCCULLAGH ET AL) 16 April 1985, columns 1-10.	1-13
Y	US, A, 4,568,666 (MCCULLAGH ET AL.) 04 February 1986, see entire document.	1-13

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
21 JULY 1995

Date of mailing of the international search report
08AUG 1995

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/04964

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. Med. Chem., Volume 36, issued 26 April 1993, K. T. Chapman et al, "Inhibition of Matrix Metalloproteinase b y N-Carboxyalkyl Peptides", pages 4293-4298, entire document.	1-13